PCT/EP2004/007820

REC'D 12 AUG 2004

WIPO PCT

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed Andrew Gerry

Dated 28 June 2004

Patents Form 1/77

Patents Act 1977
(Rule 16)

The Patent Office

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — JP/DAB/PB60390

2. Patent application number
(The Patent Office will fill in his part) — 0316290.6 — 11 JUL 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

Patents ADP number *(if you know it)* 4735870003

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — Novel Compounds

5. Name of your agent *(if you have one)* — Corporate Intellectual Property

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

Patents ADP number *(if you know it)* 8072555006

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	28
Claim(s)	2
Abstract	
Drawings	

10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application.
Signature J. Pritchard Date 11-Jul-03
J Pritchard

12. Name and daytime telephone number of person to contact in the United Kingdom: J Pritchard 01438 768610

Warning

After an application for a Patent has beeen filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission unless an application has been filed at least six weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

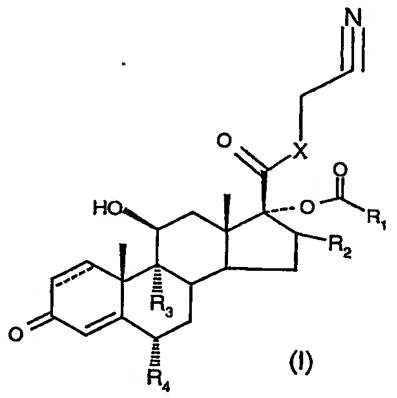
a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505
b) Write your answers in capital letters using black ink or you may type them.
c) If there is not enough space for all relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.
f) For details of the fee and ways to pay please contact the Patent Office.

Novel Compounds

The present invention relates to novel anti-inflammatory and anti-allergic compounds of the androstane series and to processes for their preparation. The present invention also relates to pharmaceutical formulations containing the compounds and to therapeutic uses thereof, particularly for the treatment of inflammatory and allergic conditions.

Glucocorticosteroids which have anti-inflammatory properties are known and are widely used for the treatment of inflammatory disorders or diseases such as asthma and rhinitis. However, we have identified a novel series of glucocorticosteroids.

Thus, according to one aspect of the invention, there is provided a compound of formula (I)



(I)

wherein

X represents O or S;

R_1 represents C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylmethyl or C_{3-8} cycloalkenyl any of which optionally may be substituted by one or more methyl groups or halogen atoms or R_1 represents aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R_2 represents hydrogen, methyl, which may be in either the α or β configuration, or methylene;

R_3 and R_4 are the same or different and each independently represents hydrogen, halogen or a methyl group;

and ⁼⁼⁼⁼ represents a single or a double bond;

and solvates thereof.

Examples of solvates include hydrates.

References hereinafter to a compound according to the invention includes both compounds of formula (I) and solvates thereof.

It will be appreciated that the invention includes within its scope all stereoisomers of the compounds of formula (I) and mixtures thereof.

Preferably, the absolute stereochemistry will be as shown in the representation of compounds of formula (I).

Preferably, X represents O.

Examples of C_{3-8} cycloalkyl groups that R_1 may represent include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl and substituted derivatives such as methylcyclopropyl (eg 1-methylcyclopropyl) and tetramethylcyclopropyl (eg 2,2,3,3-tetramethylcyclopropyl).

Examples of C_{1-6} alkyl groups that R_1 may represent include 2,2- dimethyl propyl.

Examples of C_{3-8} cycloalkylmethyl groups that R_1 may represent include cyclopentyl methyl.

Examples of C_{3-8} cycloalkenyl groups that R_1 may represent include alkenyl groups containing 1 or more double bonds (not being aromatic groups) such as cyclohexenyl eg cyclohex-2,3-enyl.

Examples of substituted aryl groups that R_1 may represent include 4-(diethylamino)sulphonylphenyl, 2,6-difluorophenyl, 4-methoxyphenyl and 4-cyano phenyl.

Examples of heteroaryl groups that R_1 may represent include quinoline-2-yl.

Examples of substituted heteroaryl groups that R_1 may represent include

5-chloro-4-methoxy-thiophene-3-yl, 2-isopropyl-1,3-thiazol-4-yl, 5-trifluoromethylfuran-2-yl, 5-methylsulphonyl-thiophene-2-yl, 5-methylthio-thiophene-2-yl and 5-ethyl-isoxazol-3-yl.

We prefer R_1 to represent C_{3-8} cycloalkyl optionally substituted by one or more methyl and/or halogen groups. We particularly prefer R_1 to represent C_{3-6} cycloalkyl, optionally substituted by one or more methyl or chlorine groups.

Most preferred groups that R_1 may represent include tetramethylcyclopropyl, cyclohexyl, and cyclopentlymethyl, especially 2,2,3,3-tetramethylcyclopropyl.

We prefer R_2 to represent methyl, especially methyl in the α configuration.

Compounds of formula (I) in which R_3 and R_4, which can be the same or different, each represents hydrogen, methyl, fluorine or chlorine, particularly hydrogen or fluorine are preferred. Especially preferred are compounds in which R_3 and R_4 are both fluorine.

Preferably, ===== represents a double bond.

It is to be understood that the present invention covers all combinations of particularly and preferred groups referred to hereinabove.

Preferred compounds of formula (I) include:

6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(2,2,3,3-tetramethycyclopropylcarbonyl)oxy-androsta-1,4-diene-17β-carbothioic acid *S*-cyanomethyl ester;

17α-(4-[(Diethylamino)sulphonyl]benzoyl)oxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid cyanomethyl ester;

17α-(5-Chloro-4-methoxy-thiophene-3-carbonyl)oxy-6α,9α-difluoro-11β-hydroxy-16α-methyl -3-oxo-androsta-1,4-diene-17β-carbothioic acid cyanomethyl ester;

6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(2,2,3,3-tetramethycyclopropylcarbonyl)oxy-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester;

17α-(Cyclohexylcarbonyl)oxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester;

6α,9α-Difluoro-17α-(2,6-difluorobenzoyl)oxy-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester;

6α,9α-Difluoro-11β-hydroxy-17α-(4-methoxybenzoyl)oxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester;

17α-(4-Cyanobenzoyl)oxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester;

17α-(Cyclopentylmethylcarbonyl)oxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester;

6α,9α-Difluoro-17α-(3,3-dimethylbutanoyl)oxy-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester;

6α,9α-Difluoro-11β-hydroxy-17α-(2-isopropyl-1,3-thiazole-4-carbonyl)oxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester;

6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(quinoline-2-carbonyl)oxy-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester;

6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(5-trifluoromethyl-furan-2-carbonyl)oxy-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester;

6α,9α-Difluoro-11β-hydroxy-16α-methyl -17α-(5-methylsulphonyl-thiophene-2-carbonyl)oxy-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester;

6α,9α-Difluoro-11β-hydroxy-16α-methyl -17α-(5-methylthio-thiophene-2-carbonyl)oxy-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester;

6α,9α-Difluoro-17α-(5-ethyl-isoxazole-3-carbonyl)oxy-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester; and

9α-Fluoro-11β-hydroxy-16β-methyl-3-oxo-17α-(2,2,3,3-tetramethylcyclopropylcarbonyl)oxy-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester.

Particularly preferred compounds are:

6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(2,2,3,3-tetramethycyclopropylcarbonyl)oxy-androsta-1,4-diene-17β-carbothioic acid *S*-cyanomethyl ester;

6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(2,2,3,3-tetramethycyclopropylcarbonyl)oxy-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester;
9α-Fluoro-11β-hydroxy-16β-methyl-3-oxo-17α-(2,2,3,3-tetramethylcyclopropylcarbonyl)oxy-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester;
17α-(Cyclohexylcarbonyl)oxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester;
17α-(Cyclopentylmethylcarbonyl)oxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester; and
6α,9α-Difluoro-17α-(3,3-dimethylbutanoyl)oxy-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester;

especially preferred are
6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(2,2,3,3-tetramethycyclopropylcarbonyl)oxy-androsta-1,4-diene-17β-carbothioic acid *S*-cyanomethyl ester; and
6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(2,2,3,3-tetramethycyclopropylcarbonyl)oxy-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester.

Most preferred is
6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(2,2,3,3-tetramethycyclopropylcarbonyl)oxy-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester.

The compounds of formula (I) have potentially beneficial anti-inflammatory or anti-allergic effects, particularly upon topical administration, demonstrated by, for example, their ability to bind to the glucocorticoid receptor and to illicit a response via that receptor. Hence, the compounds of formula (I) are useful in the treatment of inflammatory and/or allergic disorders.

Examples of disease states in which the compounds of the invention have utility include skin diseases such as eczema, psoriasis, allergic dermatitis neurodermatitis, pruritis and hypersensitivity reactions; inflammatory conditions of the nose, throat or lungs such as asthma (including allergen-induced asthmatic reactions), rhinitis

(including hayfever), nasal polyps, chronic obstructive pulmonary disease, interstitial lung disease, and fibrosis; inflammatory bowel conditions such as ulcerative colitis and Crohn's disease; and auto-immune diseases such as rheumatoid arthritis.

Compounds of the invention may also have use in the treatment of conjunctiva and conjunctivitis.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established conditions.

As mentioned above, compounds of formula (I) are useful in human or veterinary medicine, in particular as anti-inflammatory and anti-allergic agents.

There is thus provided as a further aspect of the invention a compound of formula (I) or a physiologically acceptable solvate thereof for use in human or veterinary medicine, particularly in the treatment of patients with inflammatory and/or allergic conditions.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or physiologically acceptable solvate thereof for the manufacture of a medicament for the treatment of patients with inflammatory and/or allergic conditions.

In a further or alternative aspect, there is provided a method for the treatment of a human or animal subject with an inflammatory and/or allergic condition, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) or physiologically acceptable solvate thereof.

The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions comprising a compound of formula (I) or physiologically acceptable solvate thereof together, if desirable, in admixture with one or more physiologically acceptable diluents or carriers.

Further, there is provided a process for the preparation of such pharmaceutical compositions which comprises mixing the ingredients.

The compounds according to the invention may, for example, be formulated for oral, buccal, sublingual, parenteral, local or rectal administration, especially local administration.

Local administration as used herein, includes administration by insufflation and inhalation. Examples of various types of preparation for local administration include ointments, lotions, creams, gels, foams, preparations for delivery by transdermal patches, powders, sprays, aerosols, capsules or cartridges for use in an inhaler or insufflator or drops (e.g. eye or nose drops), solutions/suspensions for nebulisation, suppositories, pessaries, retention enemas and chewable or suckable tablets or pellets (e.g. for the treatment of aphthous ulcers) or liposome or microencapsulation preparations.

Ointments, creams and gels, may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agent and/or solvents. Such bases may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil, or a solvent such as polyethylene glycol. Thickening agents and gelling agents which may be used according to the nature of the base include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, woolfat, beeswax, carboxypolymethylene and cellulose derivatives, and/or glyceryl monostearate and/or non-ionic emulsifying agents.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents or thickening agents.

Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents, suspending agents or preservatives.

Spray compositions may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain

a compound of formula (I) and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. The aerosol composition may optionally contain additional formulation excipients well known in the art such as surfactants e.g. oleic acid or lecithin and cosolvents e.g. ethanol.

Advantageously, the formulations of the invention may be buffered by the addition of suitable buffering agents.

Capsules and cartridges for use in an inhaler or insufflator, of for example gelatine, may be formulated containing a powder mix for inhalation of a compound of the invention and a suitable powder base such as lactose or starch. Each capsule or cartridge may generally contain between 20μg-10mg of the compound of formula (I). Alternatively, the compound of the invention may be presented without excipients such as lactose.

The proportion of the active compound of formula (I) in the local compositions according to the invention depends on the precise type of formulation to be prepared but will generally be within the range of from 0.001 to 10% by weight. Generally, however for most types of preparations advantageously the proportion used will be within the range of from 0.005 to 1% and preferably 0.01 to 0.5%. However, in powders for inhalation or insufflation the proportion used will be within the range of from 0.1 to 5%.

Aerosol formulations are preferably arranged so that each metered dose or "puff" of aerosol contains 20μg-2000μg, preferably about 20μg-500μg of a compound of formula (I). Administration may be once daily or several times daily, for example 2, 3, 4 or 8 times, giving for example 1, 2 or 3 doses each time. The overall daily dose with an aerosol will be within the range 100μg-10mg preferably, 200μg-2000μg. The overall daily dose and the metered dose delivered by capsules and cartridges in an inhaler or insufflator will generally be double those with aerosol formulations.

Topical preparations may be administered by one or more applications per day to the affected area; over skin areas occlusive dressings may advantageously be used. Continuous or prolonged delivery may be achieved by an adhesive reservoir system.

For internal administration the compounds according to the invention may, for example, be formulated in conventional manner for oral, parenteral or rectal administration. Formulations for oral administration include syrups, elixirs, powders, granules, tablets and capsules which typically contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, wetting agents, suspending agents, emulsifying agents, preservatives, buffer salts, flavouring, colouring and/or sweetening agents as appropriate. Dosage unit forms are, however, preferred as described below.

Preferred forms of preparation for internal administration are dosage unit forms i.e. tablets and capsules. Such dosage unit forms contain from 0.1mg to 20mg preferably from 2.5 to 10mg of the compounds of the invention.

The compounds according to the invention may in general may be given by internal administration in cases where systemic adreno-cortical therapy is indicated.

In general terms preparations, for internal administration may contain from 0.05 to 10% of the active ingredient dependent upon the type of preparation involved. The daily dose may vary from 0.1mg to 60mg, e.g. 5-30mg, dependent on the condition being treated, and the duration of treatment desired.

Slow release or enteric coated formulations may be advantageous, particularly for the treatment of inflammatory bowel disorders.

The compounds and pharmaceutical formulations according to the invention may be used in combination with or include one or more other therapeutic agents, for example selected from anti-inflammatory agents, anticholinergic agents (particularly an M_1, M_2, M_1/M_2 or M_3 receptor antagonist), other β_2-adrenoreceptor agonists, antiinfective agents (e.g. antibiotics, antivirals), or antihistamines. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with one or more other therapeutically active agents, for example selected from an anti-inflammatory agent (for example another corticosteroid or an NSAID), an anticholinergic agent, another β_2-adrenoreceptor agonist, an antiinfective agent (e.g. an antibiotic or an antiviral), or an antihistamine. Preferred are

combinations comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a β_2-adrenoreceptor agonist, and/or an anticholinergic, and/or a PDE-4 inhibitor. Preferred combinations are those comprising one or two other therapeutic agents.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, (e.g. as alkali metal or amine salts or as acid addition salts), or prodrugs, or as esters (e.g. lower alkyl esters), or as solvates (e.g. hydrates) to optimise the activity and/or stability and/or physical characteristics (e.g. solubility) of the therapeutic ingredient. It will be clear also that where appropriate, the therapeutic ingredients may be used in optically pure form.

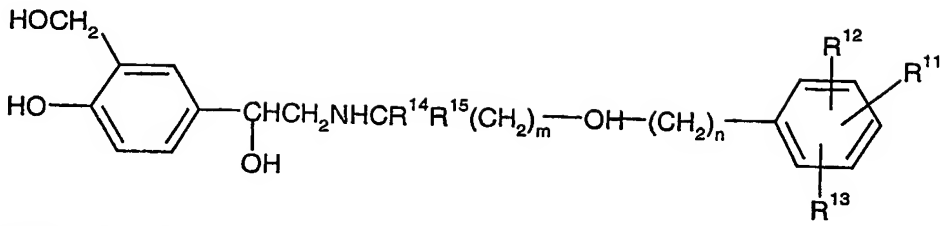
The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together with another therapeutically active agent, for example, a β_2-adrenoreceptor agonist, an anti-histamine or an anti-allergic.

A combination comprising of compound of formula (I) or a physiologically acceptable salt or solvate thereof together with a β_2-adrenoreceptor agonist is particularly preferred.

Examples of β_2-adrenoreceptor agonists include salmeterol (eg as racemate or a single enantiomer such as the R-enantiomer), salbutamol, formoterol, salmefamol, fenoterol or terbutaline and salts thereof, for example the xinafoate salt of salmeterol, the sulphate salt or free base of salbutamol or the fumarate salt of formoterol. Long-acting β_2-adrenoreceptor agonists are preferred, especially those having a therapeutic effect over a 24 hour period such as salmeterol or formoterol.

Preferred long acting β_2-adrenoreceptor agonists include those described in WO 0266 422A, WO 0227 0490, WO 0207 6933 and WO 0302 4439.

Especially preferred long-acting β_2-adrenoreceptor agonists include compounds of formula(X):



(X)

or a salt or solvate thereof, wherein:

m is an integer of from 2 to 8;

n is an integer of from 3 to 11,

with the proviso that m + n is 5 to 19,

R^{11} is $-XSO_2NR^{16}R^{17}$ wherein X is $-(CH_2)_p-$ or C_{2-6} alkenylene;

R^{16} and R^{17} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, $C(O)NR^{18}R^{19}$, phenyl, and phenyl (C_{1-4}alkyl)-,

or R^{16} and R^{17}, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring, and R^{16} and R^{17} are each optionally substituted by one or two groups selected from halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, hydroxy-substituted C_{1-6}alkoxy, $-CO_2R^{18}$, $-SO_2NR^{18}R^{19}$, $-CONR^{18}R^{19}$, $-NR^{18}C(O)R^{19}$, or a 5-, 6- or 7-membered heterocylic ring;

R^{18} and R^{19} are independently selected from hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl, and phenyl (C_{1-4}alkyl)-; and

p is an integer of from 0 to 6, preferably from 0 to 4;

R^{12} and R^{13} are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo, phenyl, and C_{1-6}haloalkyl; and

R^{14} and R^{15} are independently selected from hydrogen and C_{1-4}alkyl with the proviso that the total number of carbon atoms in R^{14} and R^{15} is not more than 4.

Suitable anti-inflammatory agents include NSAIDs.

Suitable NSAIDs include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (e.g. chemokine antagonists) or inhibitors of cytokine synthesis.

Suitable other β_2-adrenoreceptor agonists include salmeterol (e.g. as the xinafoate), salbutamol (e.g. as the sulphate or the free base), formoterol (e.g. as the fumarate), fenoterol or terbutaline and salts thereof.

Of particular interest is use of the compounds of formula (I) in combination with a phosphodiesterase 4 (PDE4) inhibitor. The PDE4-specific inhibitor useful in this aspect of the invention may be any compound that is known to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not compounds which inhibit other members of the PDE family as well as PDE4. Generally it is preferred to use a PDE4 inhibitor which has an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity. For the purposes of this disclosure, the cAMP catalytic site which binds R and S rolipram with a low affinity is denominated the "low affinity" binding site (LPDE 4) and the other form of this catalytic site which binds rolipram with a high affinity is denominated the "high affinity" binding site (HPDE 4). This term "HPDE4" should not be confused with the term "hPDE4" which is used to denote human PDE4.

A method for determining IC_{50} ratios is set out in US Patent 5,998,428, which is incorporated herein in full by reference as though set out herein. See also PCT application WO 00/57599 for another description of said assay.

The preferred PDE4 inhibitors of use in this invention will be those compounds which have a salutary therapeutic ratio, i.e., compounds which preferentially inhibit cAMP catalytic activity where the enzyme is in the form that binds rolipram with a low affinity, thereby reducing the side effects which apparently are linked to inhibiting the form which binds rolipram with a high affinity. Another way to state this is that the preferred compounds will have an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity.

A further refinement of this standard is that of one wherein the PDE4 inhibitor has an IC_{50} ratio of about 0.1 or greater; said ratio is the ratio of the IC_{50} value for competing with the binding of 1nM of [^{3}H]R-rolipram to a form of PDE4 which binds rolipram with a high affinity over the IC_{50} value for inhibiting the PDE4 catalytic activity of a form which binds rolipram with a low affinity using 1 μM[^{3}H]-cAMP as the substrate.

Most preferred are those PDE4 inhibitors which have an IC_{50} ratio of greater than 0.5, and particularly those compounds having a ratio of greater than 1.0. Preferred compounds are *cis* 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]; these are examples of compounds which bind preferentially to the low affinity binding site and which have an IC_{50} ratio of 0.1 or greater.

Other compounds of interest include:
Compounds set out in U.S. patent 5,552,438 issued 03 September, 1996; this patent and the compounds it discloses are incorporated herein in full by reference. The compound of particular interest, which is disclosed in U.S. patent 5,552,438, is *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also known as cilomalast) and its salts, esters, pro-drugs or physical forms;

AWD-12-281 from elbion (Hofgen, N. et al. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98; CAS reference No. 247584020-9); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa Hakko in WO99/16766; K-34 from Kyowa Hakko; V-11294A from Napp (Landells, L.J. et al. Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-23, Geneva) 1998] 1998, 12 (Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a pthalazinone (WO99/47505, the disclosure of which is hereby incorporated by reference) from Byk-Gulden; Pumafentrine, (-)-p-[(4*a*R*,10*b*S*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide which is a mixed PDE3/PDE4 inhibitor which has been prepared and published on by Byk-Gulden, now Altana; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from Vernalis; or T-440 (Tanabe Seiyaku; Fuji, K. et al. J Pharmacol Exp Ther,1998, 284(1): 162), and T2585.

Other possible PDE-4 and mixed PDE3/PDE4 inhibitors include those listed in WO01/13953, the disclosure of which is hereby incorporated by reference.

Suitable anticholinergic agents are those compounds that act as antagonists at the muscarinic receptor, in particular those compounds which are antagonists of the M_1 and M_2 receptors. Exemplary compounds include the alkaloids of the belladonna plants as illustrated by the likes of atropine, scopolamine, homatropine, hyoscyamine; these compounds are normally administered as a salt, being tertiary amines. These drugs, particularly the salt forms, are readily available from a number of commercial sources or can be made or prepared from literature data via, to wit: Atropine - CAS-51-55-8 or CAS-51-48-1 (anhydrous form), atropine sulfate - CAS-5908-99-6; atropine oxide - CAS-4438-22-6 or its HCl salt - CAS-4574-60-1 and methylatropine nitrate - CAS-52-88-0.

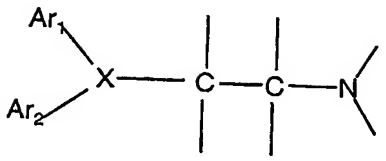
Homatropine - CAS-87-00-3, hydrobromide salt - CAS-51-56-9, methylbromide salt - CAS-80-49-9.

Hyoscyamine (*d*, *l*) - CAS-101-31-5, hydrobromide salt - CAS-306-03-6 and sulfate salt - CAS-6835-16-1.

Scopolamine - CAS-51-34-3, hydrobromide salt - CAS-6533-68-2, methylbromide salt- CAS-155-41-9.

Preferred anticholinergics include ipratropium (e.g. as the bromide), sold under the name Atrovent, oxitropium (e.g. as the bromide) and tiotropium (e.g. as the bromide) (CAS-139404-48-1). Also of interest are: methantheline (CAS-53-46-3), propantheline bromide (CAS- 50-34-9), anisotropine methyl bromide or Valpin 50 (CAS- 80-50-2), clidinium bromide (Quarzan, CAS-3485-62-9), copyrrolate (Robinul), isopropamide iodide (CAS-71-81-8), mepenzolate bromide (U.S. patent 2,918,408), tridihexethyl chloride (Pathilone, CAS-4310-35-4), and hexocyclium methylsulfate (Tral, CAS-115-63-9). See also cyclopentolate hydrochloride (CAS-5870-29-1), tropicamide (CAS-1508-75-4), trihexyphenidyl hydrochloride (CAS-144-11-6), pirenzepine (CAS-29868-97-1), telenzepine (CAS-80880-90-9), AF-DX 116, or methoctramine, and the compounds disclosed in WO01/04118, the disclosure of which is hereby incorporated by reference.

Suitable antihistamines (also referred to as H_1-receptor antagonists) include any one or more of the numerous antagonists known which inhibit H_1-receptors, and are safe for human use. All are reversible, competitive inhibitors of the interaction of histamine with H_1-receptors. The majority of these inhibitors, mostly first generation antagonists, have a core structure, which can be represented by the following formula:



This generalized structure represents three types of antihistamines generally available: ethanolamines, ethylenediamines, and alkylamines. In addition, other first generation antihistamines include those which can be characterized as based on piperizine and phenothiazines. Second generation antagonists, which are non-sedating, have a similar structure-activity relationship in that they retain the core ethylene group (the alkylamines) or mimic the tertiary amine group with piperizine or piperidine. Exemplary antagonists are as follows:

Ethanolamines: carbinoxamine maleate, clemastine fumarate, diphenylhydramine hydrochloride, and dimenhydrinate.

Ethylenediamines: pyrilamine amleate, tripelennamine HCl, and tripelennamine citrate.

Alkylamines: chlropheniramine and its salts such as the maleate salt, and acrivastine.

Piperazines: hydroxyzine HCl, hydroxyzine pamoate, cyclizine HCl, cyclizine lactate, meclizine HCl, and cetirizine HCl.

Piperidines: Astemizole, levocabastine HCl, loratadine or its descarboethoxy analogue, and terfenadine and fexofenadine hydrochloride or another pharmaceutically acceptable salt.

Azelastine hydrochloride is yet another H_1 receptor antagonist which may be used in combination with a PDE4 inhibitor.

Examples of preferred anti-histamines include methapyrilene and loratadine.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a β_2-adrenorecptor agonist.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an antihistamine.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor and a β_2-adrenoreceptor agonist.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic and a PDE-4 inhibitor.

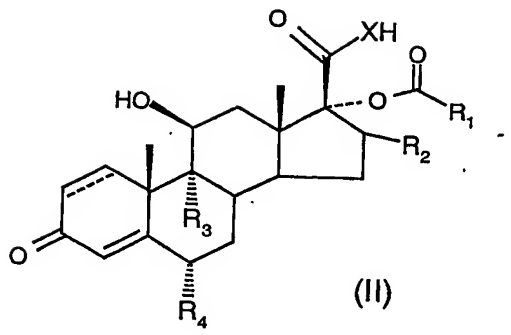
The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

The compounds of formula (I) and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

The compounds of formula (I) and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

A process according to the invention for preparing a compound of formula (I) comprises reaction of a carboxylic acid (X=O) or carbothioic acid (X=S) of formula (II)



(II)

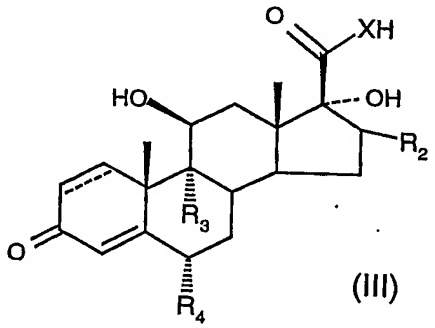
wherein R_1, R_2, R_3, R_4, X and ⁼⁼⁼ are as defined above,
with a compound of formula L-CH_2-CN wherein L represents a leaving group.

In this process the compound of formula (II) may be reacted with a compound of formula L-CH_2-CN wherein L represents a leaving group such as halogen atom or a tosyl or mesyl group or the like, under standard conditions. For example the reaction may be performed in an inert polar organic solvent e.g. N,N-dimethylformamide in the presence of a base e.g. potassium carbonate, sodium bicarbonate.

Compounds of formula (II) may conveniently be employed as salts when such salts may be prepared in crystalline form.

Compounds of formula L-CH_2-CN are either known or may be prepared by known methods.

Compounds of formula (II) may be prepared from the corresponding 17α-hydroxyl derivative of formula (III):



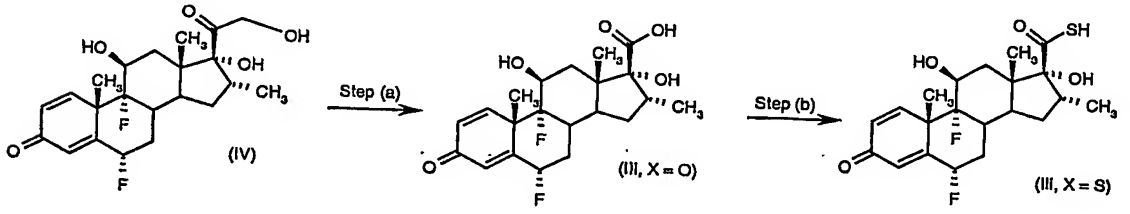
(III)

wherein X, R_2, R_3, R_4 and ⁼⁼⁼⁼ are as defined above,
using for example, the methodology described by G. H. Phillipps et al., Journal of Medicinal Chemistry, (1994), **37**, 3717-3729. The step typically comprises the addition of a reagent suitable for performing the esterification to the ester such as a compound of formula R_1COOH or an activated derivative thereof eg an activated ester, anhydride or halide thereof especially an acid halide eg the acid chloride in the presence of a mild base e.g. triethylamine. Generally the acid chloride would be employed in at least 2 times molar quantity relative to the compound of formula (III). The second mole of acid chloride tends to react with the carboxylic acid moiety in the compound of formula (III) and would need to be removed by reaction with an amine such as diethylamine or 1-methylpiperazine.

Compounds of formula (III) are either known or may be prepared in accordance with procedures described by G. H. Phillipps et al., Journal of Medicinal Chemistry, (1994), **37**, 3717-3729.

Compounds of formula (II) are new and form an aspect of the invention.

Compounds of formula (III) may also be prepared by a process comprising the following steps:



Step (a) comprises oxidation of a solution containing the compound of formula (IV) to give the carboxylic acid (III, X = O);

Preferably, step (a) will be performed in the presence of a solvent comprising methanol, water, tetrahydrofuran, dioxan or diethylene glygol dimethylether. For example, so as to enhance yield and throughput, preferred solvents are methanol, water or tetrahydrofuran, and more preferably are water or tetrahydrofuran, especially water and tetrahydrofuran as solvent. Dioxan and diethylene glygol dimethylether are also preferred solvents which may optionally (and preferably) be

employed together with water. Preferably, the solvent will be present in an amount of between 3 and 10vol relative to the amount of the starting material (1wt.), more preferably between 4 and 6 vol., especially 5 vol. Preferably the oxidising agent is present in an amount of 1-9 molar equivalents relative to the amount of the starting material. For example, when a 50% w/w aqueous solution of periodic acid is employed, the oxidising agent may be present in an amount of between 1.1 and 10wt. relative to the amount of the starting material (1wt.), more preferably between 1.1 and 3wt., especially 1.3wt. Preferably, the oxidation step will comprise the use of a chemical oxidising agent. More preferably, the oxidising agent will be periodic acid or iodic acid or a salt thereof. Most preferably, the oxidising agent will be periodic acid or sodium periodate, especially periodic acid. Alternatively (or in addition), it will also be appreciated that the oxidation step may comprise any suitable oxidation reaction, eg. one which utilises air and/or oxygen. When the oxidation reaction utilises air and/or oxygen, the solvent used in said reaction will preferably be methanol. Preferably, step (a) will involve incubating the reagents at room temperature or a little warmer, say around 25 °C eg for 2 hours. The compound of formula (V) may be isolated by recrystallisation from the reaction mixture by addition of an anti-solvent. A suitable anti-solvent for compound of formula (V) is water. Surprisingly we have discovered that it is highly desirable to control the conditions under which the compound of formula (V) is precipitated by addition of anti-solvent eg water. When the recrystallisation is performed using chilled water (eg water/ice mixture at a temperature of 0-5 °C) although better anti-solvent properties may be expected we have found that the crystalline product produced is very voluminous, resembles a soft gel and is very difficult to filter. Without being limited by theory we believe that this low density product contains a large amount of solvated solvent within the crystal lattice By contrast when conditions of around 10 °C or higher are used (eg around ambient temperature) a granular product of a sand like consistency which is very easily filtered is produced. Under these conditions, crystallisation typically commences after around 1 hour and is typically completed within a few hours (eg 2 hours). Without being limited by theory we believe that this granular product contains little or no of solvated solvent within the crystal lattice.

Step (b) will typically comprise the addition of a reagent suitable for converting the carboxylic acid (III, X = O) into the carbothioic acid (III, X = S) eg. using hydrogen sulphide gas together with a suitable coupling agent eg. carbonyldiimidazole (CDI) in the presence of a suitable solvent eg. dimethylformamide.

Solvates of compounds of formula (I) which are not physiologically acceptable may be useful as intermediates in the preparation of compounds of formula (I) or physiologically acceptable solvates thereof.

Compounds of formula (I) and/or solvates thereof demonstrate good anti-inflammatory properties, with predictable pharmacokinetic and pharmacodynamic behaviour. They also have an attractive side-effect profile, demonstrated, for example, by increased selectivity for the glucocorticoid receptor over the progesterone receptor and/or increased selectivity for glucocorticoid receptor mediated transrepression over transactivation and are compatible with a convenient regime of treatment in human patients.

The following non-limiting Examples illustrate the invention:

EXAMPLES

General

Chromatographic purification was performed using pre-packed Bond Elut silica gel cartridges available commercially from Varian or by flash chromatography on pre-packed Biotage silica columns. These cartridges were pre-conditioned with dichloromethane prior to use. LCMS was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID) eluting with 0.1% HCO_2H and 0.01 M ammonium acetate in water (solvent A), and 0.05% HCO_2H 5% water in acetonitrile (solvent B), using the following elution gradient 0-0.7 min 0%B, 0.7-4.2 min 100%B, 4.2-5.3 min 0%B, 5.3-5.5 min 0%B at a flow rate of 3 ml/min. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive and negative mode (ES+ve and ES-ve).

Intermediates

Intermediate 1: 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(2,2,3,3-tetramethycyclopropylcarbonyl)oxy-androsta-1,4-diene-17β-carbothioic acid

Oxalyl chloride (3ml, 34.9mmol) was added to a stirred and cooled (ice) solution of 2,2,3,3-tetramethylcyclopropyl carboxylic acid (2.48g, 17.45mmol) in dry dichloromethane (70ml) containing diethylformamide (2drops) and the mixture stirred for 3h. The solvent was evaporated and residual acid chloride was redissolved in

dichloromethane (15ml) and added to a stirred and cooled (ice) solution of 6α,9α-difluoro-11β,17α-dihydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid (G. H. Phillipps et al., (1994) Journal of Medicinal Chemistry, **37**, 3717-3729) (3g, 7.27mmol) in dichloromethane (120ml) containing triethylamine (2.03ml, 14.5mmol). The mixture was allowed to warm to room temperature and after 1.5h was washed successively with aqueous sodium bicarbonate (150ml), 1M hydrochloric acid (150ml) and brine (150ml) and dried through a hydrophobic frit and evaporated. The residual solid was dissolved in dioxane (140ml) and 1-methylpiperazine (3.23ml, 29.1mmol) was added and the mixture stirred for 4h. The mixture was then added slowly to a vigorously stirred mixture of 2M hydrochloric acid (200ml) and ice (200ml). The mixture was extracted with dichloromethane (300ml) and the extract washed with water and dried through a hydrophobic frit and evaporated. This material was dissolved in dioxane (80ml) and treated again with 1-methylpiperazine (3.23ml) for 20h. The mixture was added slowly to a vigorously stirred mixture of 2M hydrochloric acid (200ml) and ice (200ml). The mixture was extracted with dichloromethane (300ml) and the extract washed with water and dried through a hydrophobic frit and evaporated. Purification by chromatography on a 90g biotage cartridge using initially cyclohexane and finally cyclohexane:ethyl acetate (3:1) yielded the title compound (1.33g): LCMS retention time 3.99 min.

Intermediate 2: 17α-(4-[(Diethylamino)sulphonyl]benzoyl)oxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid

4-[(Diethylamino)sulphonyl]benzoyl chloride (134mg) was added to a stirred solution of 6α,9α-difluoro-11β,17α-dihydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid (200mg) in pyridine (8ml) and the mixture stirred under nitrogen for 2h. More acid chloride (134mg) was the mixture stirred for a further 2h. 6M HCl (60ml) was then added and the mixture extracted with ethyl acetate (3x30ml). The combined organnic extracts were washed with 2M HCl (30ml), dried through a hydrophobic frit and evaporated to give the title compound as a white foam: LCMS retention time 4.26min.

Intermediate 3: 17α-(5-Chloro-4-methoxy-thiophene-3-carbonyl)oxy-6α,9α-difluoro-11β-hydroxy-16α-methyl -3-oxo-androsta-1,4-diene-17β-carbothioic acid

Prepared using methods similar to that described for Intermediate 2. LCMS retention time 4.06 min.

Intermediate 4: 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(2,2,3,3-tetramethycyclopropylcarbonyl)oxy-androsta-1,4-diene-17β-carboxylic acid
Prepared using methods similar to that described for Intermediate 1.
LCMS retention time 3.59 min.

Intermediate 5: 17α-(Cyclohexylcarbonyl)oxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid
Cyclohexanecarbonyl chloride (0.081ml, 0.6mmol) was added to a stirred and cooled (ice) solution of 6α,9α-difluoro-11β,17α-dihydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid (G. H. Phillipps et al., (1994) Journal of Medicinal Chemistry, **37**, 3717-3729) (200mg, 0.5mmol) in pyridine (3ml) and the mixture stirred for 2h and then poured into 2M HCl. The mixture was extracted twice with ethyl acetate and the combined organic extracts were washed successively with 2M HCl and brine and evaporated to give the title compound (296mg): LCMS retention time 3.67 min.

Intermediate 6: 6α,9α-Difluoro-17α-(2,6-difluorobenzoyl)oxy-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid
Prepared using methods similar to that described for Intermediate 5. LCMS retention time 3.45 min.

Intermediate 7: 6α,9α-Difluoro-11β-hydroxy-17α-(4-methoxybenzoyl)oxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid
Prepared using methods similar to that described for Intermediate 5. LCMS retention time 3.38 min.

Intermediate 8: 17α-(4-Cyanobenzoyl)oxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid
Prepared using methods similar to that described for Intermediate 5. LCMS retention time 3.36 min.

Intermediate 9: 17α-(Cyclopentylmethylcarbonyl)oxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid
Prepared using methods similar to that described for Intermediate 5. LCMS retention time 3.65 min.

Intermediate 10: 6α,9α-Difluoro-17α-(3,3-dimethylbutanoyl)oxy-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid
Prepared using methods similar to that described for Intermediate 5. LCMS retention time 3.46 min.

Intermediate 11: 6α,9α-Difluoro-11β-hydroxy-17α-(2-isopropyl-1,3-thiazole-4-carbonyl)oxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid
Prepared using methods similar to that described for Intermediate 5. LCMS retention time 3.38 min.

Intermediate 12: 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(quinoline-2-carbonyl)oxy-androsta-1,4-diene-17β-carboxylic acid
Prepared using methods similar to that described for Intermediate 5. LCMS retention time 3.46 min.

Intermediate 13: 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(5-trifluoromethyl-furan-2-carbonyl)oxy-androsta-1,4-diene-17β-carboxylic acid
Prepared using methods similar to that described for Intermediate 5. LCMS retention time 3.61 min.

Intermediate 14: 6α,9α-Difluoro-11β-hydroxy-16α-methyl -17α-(5-methylsulphonyl-thiophene-2-carbonyl)oxy-3-oxo-androsta-1,4-diene-17β-carboxylic acid
Prepared using methods similar to that described for Intermediate 5. LCMS retention time 3.28 min.

Intermediate 15: 6α,9α-Difluoro-11β-hydroxy-16α-methyl -17α-(5-methylthio-thiophene-2-carbonyl)oxy-3-oxo-androsta-1,4-diene-17β-carboxylic acid
Prepared using methods similar to that described for Intermediate 5. LCMS retention time 3.69 min.

Intermediate 16: 6α,9α-Difluoro-17α-(5-ethyl-isoxazole-3-carbonyl)oxy-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid
Prepared using methods similar to that described for Intermediate 5. LCMS retention time 3.45 min.

Intermediate 17: 9α-Fluoro-11β-hydroxy-16β-methyl-3-oxo-17α-(2,2,3,3-tetramethylcyclopropylcarbonyl)oxy-androsta-1,4-diene-17β-carboxylic acid

Prepared from 11β,17α-dihydroxy-9α-fluoro-16β-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid (G. H. Phillipps et al., (1994) Journal of Medicinal Chemistry, **37**, 3717-3729) and 2,2,3,3-tetramethylcyclopropyl carbonyl chloride using methods similar to that described for Intermediate 2. LCMS retention time 3.75 min.

Examples

Example 1: 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(2,2,3,3-tetramethycyclopropylcarbonyl)oxy-androsta-1,4-diene-17β-carbothioic acid *S*-cyanomethyl ester

Bromoacetonitrile (0.042ml, 0.6mmol) was added to a stirred and cooled (ice) solution of Intermediate 1 (120mg, 0.22mmol) and sodium hydrogen carbonate (21mg, 0.245mmol) in DMF (3ml) under nitrogen and the mixture stirred at room temperature for 18h. Diethylamine (0.03ml, 0.29mmol) was added and the mixture stirred for 15min when 2M HCl (4ml) and then water (5ml) and dichloromethane (5ml) were added. The organic phase was separated washed successively with aqueous sodium hydrogen carbonate (5ml) and brine (5ml) and dried through a hydrophobic frit and evaporated to dryness. Purification on a Bon Elut cartridge using initially cyclohexane and finally cyclohexane:ethyl acetate 3:1 gave the title compound (86mg): LCMS retention time 3.82 min, *m/z* 576 MH^+

Example 2: 17α-(4-[(Diethylamino)sulphonyl]benzoyl)oxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid cyanomethyl ester

Example 2 was prepared from Intermediate 2 using a method similar to that described for Example 1. LCMS retention time 3.62 min, *m/z* 691 MH^+

Example 3: 17α-(5-Chloro-4-methoxy-thiophene-3-carbonyl)oxy-6α,9α-difluoro-11β-hydroxy-16α-methyl -3-oxo-androsta-1,4-diene-17β-carbothioic acid cyanomethyl ester

Example 3 was prepared from Intermediate 3 using a method similar to that described for Example 1. LCMS retention time 3.58 min, *m/z* 626/628 MH^+

Example 4: 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(2,2,3,3-tetramethycyclopropylcarbonyl)oxy-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester

Bromoacetonitrile (0.229ml, 3.29mmol) was added to a stirred and cooled (ice) solution of Intermediate 4 (634mg, 1.22mmol) and sodium carbonate (1.29g, 12.2mmol) in DMF (15ml) under nitrogen and the mixture stiirred at room temperature for 2h. More sodium carbonate (258mg) was added and the mixture stirred for a further 18h. 2M HCl (20ml) was added dropwise follwed by water (25ml) and the mixture was extracted with ethyl acetate (2x50ml). The combined organic extracts were washed successively with aqueous sodium hydrogen carbonate (50ml) and brine (50ml) and dried through a hydrophobic frit and evaporated to dryness. Purification on a Bon Elut cartridge using initially cyclohexane and finally cyclohexane:ethyl acetate 3:1 gave the title compound as a white solid (485mg): LCMS retention time 3.79 min, *m/z* 560 MH^+

Example 5: 17α-(Cyclohexylcarbonyl)oxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester

Example 5 was prepared from Intermediate 5 using a method similar to that described for Example 4. LCMS retention time 3.65 min, *m/z* 546 MH^+

Example 6: 6α,9α-Difluoro-17α-(2,6-difluorobenzoyl)oxy-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester

Example 6 was prepared from Intermediate 6 using a method similar to that described for Example 4. LCMS retention time 3.48 min, *m/z* 576 MH^+

Example 7: 6α,9α-Difluoro-11β-hydroxy-17α-(4-methoxybenzoyl)oxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester

Example 7 was prepared from Intermediate 7 using a method similar to that described for Example 4. LCMS retention time 3.53 min, *m/z* 570 MH^+

Example 8: 17α-(4-Cyanobenzoyl)oxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester

Example 8 was prepared from Intermediate 8 using a method similar to that described for Example 4. LCMS retention time 3.44 min, *m/z* 565 MH^+

Example 9: 17α-(Cyclopentylmethylcarbonyl)oxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester

Example 9 was prepared from Intermediate 9 using a method similar to that described for Example 4. LCMS retention time 3.69 min, *m/z* 546 MH^+

Example 10: 6α,9α-Difluoro-17α-(3,3-dimethylbutanoyl)oxy-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester

Example 10 was prepared from Intermediate 10 using a method similar to that described for Example 4. LCMS retention time 3.60 min, *m/z* 534 MH^+

Example 11: 6α,9α-Difluoro-11β-hydroxy-17α-(2-isopropyl-1,3-thiazole-4-carbonyl)oxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester

Example 11 was prepared from Intermediate 11 using a method similar to that described for Example 4. LCMS retention time 3.50 min, *m/z* 589 MH^+

Example 12: 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(quinoline-2-carbonyl)oxy-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester

Example 12 was prepared from Intermediate 12 using a method similar to that described for Example 4. LCMS retention time 3.61 min, *m/z* 591 MH^+

Example 13: 6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(5-trifluoromethyl-furan-2-carbonyl)oxy-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester

Example 13 was prepared from Intermediate 13 using a method similar to that described for Example 4. LCMS retention time 3.72 min, *m/z* 598 MH^+

Example 14: 6α,9α-Difluoro-11β-hydroxy-16α-methyl -17α-(5-methylsulphonyl-thiophene-2-carbonyl)oxy-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester

Example 14 was prepared from Intermediate 14 using a method similar to that described for Example 4. LCMS retention time 3.29 min, *m/z* 624 MH^+

Example15: 6α,9α-Difluoro-11β-hydroxy-16α-methyl -17α-(5-methylthio-thiophene-2-carbonyl)oxy-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester

Example 15 was prepared from Intermediate 15 using a method similar to that described for Example 4. LCMS retention time 3.64 min, *m/z* 592 MH^+

Example 16: 6α,9α-Difluoro-17α-(5-ethyl-isoxazole-3-carbonyl)oxy-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester

Example 16 was prepared from Intermediate 16 using a method similar to that described for Example 4. LCMS retention time 3.44 min, *m/z* 559 MH^+

Example 17: 9α-Fluoro-11β-hydroxy-16β-methyl-3-oxo-17α-(2,2,3,3-tetramethylcyclopropylcarbonyl)oxy-androsta-1,4-diene-17β-carboxylic acid cyanomethyl ester

Example 17 was prepared from Intermediate 17 using a method similar to that described for Example 4. LCMS retention time 3.77 min, *m/z* 542 MH^+

Pharmacological Activity

Pharmacological activity may be assessed in functional in vitro assays of glucocorticoid agonist activity.

The functional assay based on that described by K.P.Ray et al., Biochem J. (1997), **328**, 707-715 provides a measure of transrepressive activity of a glucocorticoid agonist. A549 cells stably transfected with a reporter gene containing the NF-κB responsive elements from the ELAM gene promoter coupled to sPAP (secreted alkaline phosphatase) are treated with test compounds at appropriate doses for 1 hour at 37°C. The cells are then stimulated with tumour necrosis factor (TNF, 10ng/ml) for 16 hours, at which time the amount of alkaline phosphatase produced is measured by a standard colourimetric assay. Dose response curves are constructed from which EC_{50} values may be estimated.

The EC_{50} values for compounds of Examples 1 to 17 were < 10nM.

The functional assay based on that described by R.J.H. Austin et al., Eur Resp J. (2002), **20**,1386-1392 measures the ability of compounds to directly transactivate gene expression. A549 cells stably transfected with a reporter gene containing the glucocorticoid responsive region of the mouse mammary tumour virus long terminal repeat (MMTV-LTR) coupled to renilla luciferase were treated with test compounds at appropriate doses for 6 hour at 37°C. The amount of luciferase activity present

within the cells is then determined by measuring the light emitted following incubation with a suitable substrate. Dose response curves were constructed from which EC_{50} values were estimated and from which maximal responses are calculated relative to Dexamethasone (100%).

Compound of Examples 1, 4, 5, 9, 10 and 17 showed maximal responses of <20 % in this assay.

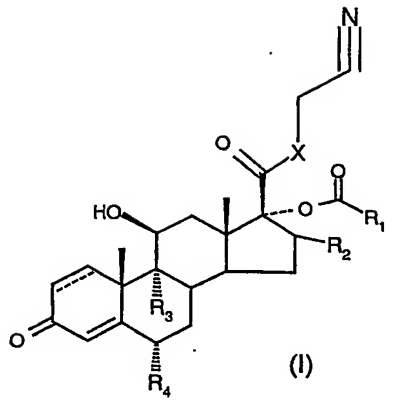
Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims.

The patents and patent applications described in this application are herein incorporated by reference.

CLAIMS

1. A compound of formula (I):



(I)

wherein

X represents O or S;

R_1 represents C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkylmethyl or C_{3-8} cycloalkenyl any of which optionally may be substituted by one or more methyl groups or halogen atoms or R_1 represents aryl, substituted aryl, heteroaryl or substituted heteroaryl;

R_2 represents hydrogen, methyl, which may be in either the α or β configuration, or methylene;

R_3 and R_4 are the same or different and each independently represents hydrogen, halogen or a methyl group;

and ⁼⁼⁼⁼ represents a single or a double bond;

and solvates thereof.

2. A compound of formula (I) as defined in claim 1 or a physiologically acceptable solvate thereof for use in veterinary or human medicine.

3. Use of a compound of formula (I) as defined in claim 1 or a physiologically acceptable solvate thereof for the manufacture of a medicament for the treatment of inflammatory and/or allergic conditions.

4. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 or a physiologically acceptable solvate thereof together, if desirable, in admixture with one or more physiologically acceptable diluents or carriers.

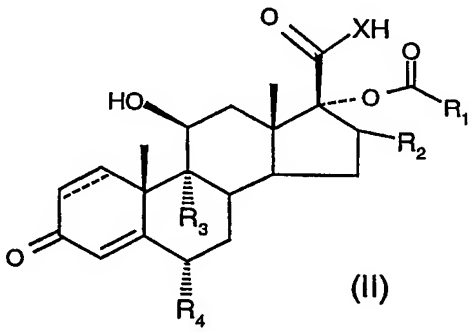
5. A pharmaceutical aerosol formulation comprising a compound of formula (I) as defined in claim 1 or a physiologically acceptable solvate thereof, and a fluorocarbon or hydrogen-containing chlorofluoro carbon as propellant, optionally in combination with a surfactant and/or a cosolvent.

6. A pharmaceutical composition according to claim 4 or 5 which further comprises another therapeutically active agent.

7. A pharmaceutical composition according to claim 6 in which said another therapeutically active agent is a β_2-adrenoreceptor agonist.

8. A method for the treatment of a human or animal subject with an anti-inflammatory and/or allergic condition, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) as defined in claim 1 or a physiologically acceptable solvate thereof.

9. A compound of formula (II)



(II)

wherein X, R_1, R_2, R_3, R_4 X and ===== are as defined above